SECOND SERIES VOL. IX, No. 7

BULLETIN

OF

THE NEW YORK ACADEMY OF MEDICINE

INCORPORATED 1851

JULY, 1933

PUBLISHED MONTHLY BY

THE NEW YORK ACADEMY OF MEDICINE

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New York, N. Y.

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Entered as second-class matter, February 3, 1928,
at the Post Office at New York, N. Y., under the Act of August 24, 1912.
Subscription $2.00 per year. Single copies, 25 cents.

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EDITORIAL

THE SKIN AS A FUNCTIONAL ORGAN OF THE BODY[1]

Early in the 19th century, the skin came to be regarded as a physiological organ of the body. Its four principal functions were known from classical antiquity; but physicians did not begin to act upon this assumption until latterly. The cell theory, as elaborated by Virchow, with reference to pathological formations, was the starting point of modern reasoning about the skin. Virchow, a champion of democracy within the Prussian state, conceived of the body as a kind of political organization of highly differentiated citizen-cells, some, as in the heart, or lungs, carrying on the scheme of division of labor as skilled employees in a closed industrial area or unit; others, such as neoplasms, constituting anti-social, non-industrial groups, subsisting as parasites at the expense of the social body; others, like cancer, being lawless, anarchistic elements, running counter to social welfare, and sometimes proliferating to the extent of destroying the whole social organization. Democracy, in one well-known view, is not so much a form of government as a mode of education of the people for future social and political adjustments. Government, whether of a hamlet, a city or a vast area like the United States or Russia, is not a matter of differentiation, as in the cell state, but of integration or balance of centrifugal and centripetal social forces, of debit

[1]Lecture read in the Institute of the History of Medicine, Welch Medical Library, Baltimore, Maryland, on April 12, 1933.

and credit, of community welfare and independence, of the altruistic and self-regarding motives. Even the financing or feeding of an army, a city or a nation is a matter of integration, since either tyranny or anarchy in such relations may spell chaos. Beaconsfield observed that where social solidarity and cooperation are very strong, government, as such, may be unobtrusive to the vanishing point; where the social order is weak, in other words, centrifugal and heterodox, strong government is necessary. Bismarck adapted himself to the *panta rhei* view of things and inscribed upon his seal ring *unda fert nec regitur.* There is no better example of the theory that the best government governs least than the human or animal body. So well balanced and integrated are its different physiologic units, circulatory, digestive, respiratory, nervous, endocrine, that we are not even aware of their existence until they get out of order. The function of the body, as a closed physicochemical system, is to maintain a certain constant balance of all these units with reference to one another and to the external world. An automatic balance of this kind constitutes health; imbalance disease. The immense groups of citizen-cells, each of them with an intense, individualistic life of its own, constitute the locus, in each case, of balance or imbalance within each unit or among the several units with reference to the whole organism. Nevertheless, the significance of the skin as a physiologic organ of the body, as an analogue of the heart, the lungs or the nervous system, is best understood by considering, for a moment, the individual cell.

In the beginning was protoplasm, without form and void, a structureless colloid mass, neither alive nor dead, but chemically active, and tending to concentrate at a "center of oxidation", through the establishment of chemical equilibrium between the periphery of the colloid and the investing medium. If this mass were floating in sea water, then the surface of discontinuity between the rim of the protoplasm and the investing saline medium would be the locus of formation of a new chemical substance at the interface and according to the thermodynamic laws gov-

erning the formation of liquid films, the only stable substance which could be so evolved would be the one having the least relative surface tension. It is only when the colloid acquires this limiting, semi-permeable envelope or cell-membrane, that it can be regarded as alive, in the sense of acquiring, shall we say, by act of God, the physiological functions of nutrition, metabolism and reproduction. It is only when the center of oxidation becomes similarly invested that it can function as the cell nucleus and carry on cell division. It is through the existence of this peripheral, semi-permeable envelope that a mass of nucleated or oxidating protoplasm, an organ or an organism becomes vitalized, for even blood-serum, milk, chyle, the pleural, pericardial, peritoneal, synovial and cerebrospinal fluids are physiologically dead, albeit chemically active, or more accurately, passive. In the infant, the skin weighs one-fifth of the body, in the adult 18 per cent. The epidermis weighs a pound. In the larger creatures, such as the crocodile, the tiger or the python, this protective envelope becomes extraordinarily thick and tough, merging even into the hard carapace of the turtle or such appendages of the skin as claws, hoofs, horns, tusks, nails, hair and wool, which only begin to be alive at their proximal extremities[2]. Nothing animate or inanimate, from a protoplasmic cell to jacketed steam, can function, in the sense of doing work through proper channels, without an investing envelope, which is an analogue of the protective mechanisms of a nation with reference to the *propter invidiam* of other nations. In the view of Lord Kelvin, the living organism functions, not as a thermodynamic engine, but like an electric motor energized by a voltaic battery. In the view of Sir Oliver Lodge, the function of life, vitality or the "vital principal" is not to generate this energy, but to guide it into proper channels, as the steam in the engine is canalized to do work. Only a small amount of the free energy generated is available to do this work, and but for

[2]See, the interesting contribution of A. F. A. King, "What is a living animal? How much of it is alive?" in *Popular Science Monthly*, N. Y., 1909, LXXV, 289-296.

the limiting envelope, the total energy, say in the boiler, would be dissipated into space. So, too, an animal flayed of its hide, let alone a human being, would not last long. In ancient Rome, statues of Apollo flaying Marsyas stood in front of the Forum and other courts of justice, to symbolize the omnipotence of the law in inflicting punishment. Whether it would be possible to remove such a thin, fragile, sensitive envelope as the human skin, except inchmeal, is dubious, but if so, the attitude of the victim in his death agony would not be passive but more probably like that of cadavers of people burned to death in conflagrations, the *attitude de combat* of the medico-legal experts. Physicists have found that the human skin, as an insulator to prevent this dissipation of vital energy, has an electrical resistance between 1000 and 6000 ohms. That of a horse's hoof is 4,700,000,000 ohms, that of a green pea ten million ohms, that of a grain of wheat between two million and ten trillion ohms[3]. Apart from microorganisms, the human skin is therefore the most sensitive and frangible of all integuments or protective envelopes in animals and plants.

These facts may serve to illustrate the extreme importance of the skin as a functional organ of the body. In the light of Galen's view that "structure follows function", the limiting envelope, say of a primordial cell, came into being through a physico-chemical determinism or necessity. In Haller's day, physiology became "animated anatomy", or structure in the act of functioning, but it took years to arrive at our present view of pathology as an alteration or deflection of physiologic function. What has hindered progress has been the confusion of the functioning structure itself with the physiologic determinism which created it and keeps it going in definite channels. As Huxley observed, the cells "are no more the producers of the vital phenomena than the shells scattered along the sea beach are the instruments by which the gravitative force of the moon acts upon the ocean. Like these,

[3]King: *op. cit.*, 292-294.

the cells mark only where the vital tides have been and how they acted." It is comparatively easy to visualize how life may have arisen from a colloid accidentally charged with electricity and how it keeps going by what Hering called the "facultative memory" of protoplasm, the power to go on doing what it learned to do in the first remote instance; but just why all this came to pass we shall never know.

Human concern as to the individuality, vitality and integrity of the skin is evidenced in innumerable by-words and literary expressions from the earliest times. That "beauty is only skin deep" is suggested at once by the cosmetic episodes on Greek vases, the multifarious touting of cold creams and cosmetics in current magazines or the various allusions to somebody's "stale skin" in recent novels. Lecky opined that, in the general run of humanity, this cutaneous phase of facial comeliness is largely a matter of color and texture, while the aristocratic profile is an affair of bony conformation. In Richardson's *Clarissa Harlowe* (1748), we read: "Her features are so regular that were she only skin and bone, she must be a beauty;" and in *Middlemarch* (I, 9): "He looks like a death's head skinned over for the occasion." Huxley even made color of skin the criterion of race ("Race is pigmentation"), albeit the cranial characteristics of the three fundamental ethnic groups are vividly outlined in bas-relief on the Egyptian tomb of Seti. That a man is as old as his skin, as well as his arteries, is a very old physiologic observation[4]. Kipling's trite pronouncement that women are the same thing under their skins may be set off by the more scientific observation of Persius (III, 30): *Ego te intus et in cute novi,*

[4]Retterer (*Compt. rend. Soc. de biol.*, Paris, 1916, LXXIX, 1113-1118) regards the epithelium as a kind of reserve bank of potential energy of the organism, a sort of fountain of youth for the other tissues, as long as it continues to proliferate. In childhood, youth and middle life, the dermal envelope renews itself at the expense of the proliferating epidermal epithelium. In old age, when the epithelium ceases to proliferate, the epidermis dwindles and the skin wrinkles to the point of senile atrophy. The Greek and Latin words for old age and for the skin sloughed off by a snake are identical.

which is the essence of the physician's approach in diagnosis. The ancient writers, indeed, abound in acute observations on the skin, such as the *facies Hippocratica* or Lucretius (VI, 1193) on the *frigida pellis* of approaching death; or Horace on the well-groomed appearance of those who take proper care of their persons:

"Me pinguem et nitidem bene curata cute visis," I, Epist., IV, 15.

or of the fop:

"In cute curanda plus aequo operata juventus," I, Epist., II, 29.

or the plebian hide of the churlish rough-neck:

"Quae se commendat tonsa cute dentibus atris," I, Epist., XVIII, 7.

or the whited sepulchre sometimes implicit in a comely exterior:

"Introrsum turpem, speciosum pelle decora," I, Epist., XVI, 45.

In the daily personal hygiene of the Greeks and Romans, oiling of the skin, the use of the strigil or skin-scraper and the practice of depilation by professionals, were routine features.

Such expressions of the English people as thick and thin skinned, to be in one's skin, to be in a bad skin (bad temper), to be fond of one's own skin, to come off with a whole skin, or the impossibility of jumping out of one's skin, go back to the *veterem pelliculam retines* of Persius (V, 116) and the *quiescere in propria pelle* of Martial (V, 60). Horace notes the revelation of character implied in stripping off the facial mask as *detrahere pellem* (II Sat. I, 64). "As honest as the skin between your brows" was a common expression of Shakespeare and the old dramatists to denote how much the skin is an essential element of one's being, indeed, the significance of the skin as an *arrêt irrevocable* of destiny is a commonplace in Jeremiah (XIII, 23): "Can the Ethiopian change his skin or the leopard his spots?" In the tropical and subtropical Orient, any wound or lesion of the skin is a matter of moment or concern, as being hard

to heal. The dubious relation of the skinning over of a wound to perfect healing is implicit in Coleridge's line:

"Short peace shall skin the wounds of causeless war."

Oriental feeling about this matter is plain in the book of Job:

"My skin is broken and become loathsome" (VII, 7).

"Destruction shall be ready at his side and it shall devour the strength of his skin" (XVIII, 12-13).

"My bone cleaveth to my skin and to my flesh and I am escaped with the skin of my teeth" (XIX, 20).

The pathological effects of tropical fever and famine in old age are poignantly conveyed in Job (XXX, 29-30):

"I am a brother to dragons and a companion to owls;
My skin is black upon me and my bones are burned with heat;"

and in the Lamentations of Jeremiah:

"Our skin was black like an oven from the terrible famine" (V, 10).

"My flesh and my skin he hath made old; he hath broken my bones" (III, 4).

"Their skin cleaveth to their bones; it is withered; it is become like a stick" (IV, 8).

The fifty nine verses of the 13th chapter of Leviticus, on the ritual examination and isolation of lepers and suspects of leprosy, are replete with clinical casuistry based upon appearances of the skin:

"When a man shall have in the skin of his flesh a rising, a scab, or bright spot, and it be in the skin of his flesh like the plague of leprosy; then he shall be brought unto Aaron the priest, or unto one of his sons the priests:

"And the priest shall look on the plague in the skin of the flesh: and when the hair in the plague is turned white, and the plague in sight be deeper than the skin of his flesh, it is a plague of leprosy: and the priest shall look on him, and pronounce him unclean.

"If the bright spot be white in the skin of his flesh, and in sight be not deeper than the skin, and the hair thereof be not turned white: then the priest shall shut up him that hath the plague seven days."

The general concern of humanity about the integrity of the skin is voiced by Satan in the book of Job (II, 4):

"Skin for skin, yea, all that a man hath will he give for his life;"

as well as in the jolly outburst of the Host in the Merry Wives of Windsor (III, 1):

"Your hearts are mighty, your skins are whole."

Little was really known about the structure of the skin until the establishment of the cell theory, although observations on the coarser histology, the end organs, the pores and the perspiration had been made in the earlier period by Fabricius ab Aquapendente (1618), Malpighi (1665), Bartholinus (1666), Leuuwenhoek (1674), Albinus (1685), Morgagni (1706), Vater (1717), Boerhaave (1738) and J. F. Meckel (1753-7). The rest was done by such promoters of the cell theory as Purkinje (1833), Henle (1840), von Baerensprung (1848), Kölliker (1852), Lister (1852), Meissner (1853), Langerhans (1858-73), Huxley (1859), Bizzozero (1864), Vulpian (1871-9), Friedrich Merkel (1875-81), Unna (1876-1908), Ranvier (1877-80), Krause (1880-), Flemming (1881-4) and Hebra (1882). There was much writing on the ethnic peculiarities of the skin, particularly in the negro, down to the time of Soemmerring (1785) and even of Flourens (1837). With the cell theory, it came to be known that, in the unicellular organisms and protozoa, the cell membrane is the peripheral agent in nutrition, excretion and the molar phase of reproduction. In man, the tactile, excretory, absorptive and protective functions of the skin were known from the earliest times. Hippocrates and Galen assumed that the skin is permeable to air and the quantitative balance between perspiration, urination and alvine excretion was a matter of daily and seasonal observation. The rôle of the skin in tissue respiration was established by Spallanzani for amphibia (*circa* 1798)[5]; by Lavoisier (1777), Cruikshank (1779-95), Abernethy (1793), Seguin (1814), Aubert and Lange (1872) for man; and by Zuntz, Lehmann and Hagemann for the total skin of a horse (1894). Spallanzani showed that many amphibia take up oxygen and give off CO_2 by

[5]Spallanzani: Memorie sulla respirazione, Milano, 1803 (posthumous publication).

the skin after excision of the lungs and live longer than the same animals whose skin has been varnished. Lavoisier and Cruikshank found that the human skin excretes CO_2 and Abernethy that it will absorb oxygen and give off CO_2 as readily in the air as in oxygen. Eventually Pflüger and his pupils (1875-93) established the truth of Spallanzani's discovery that gas-exchange in the tissues is greater than that in the blood. Fatalities in earlier experiments on varnishing the human skin, such as that of the boy gilded as an angel at the coronation of Pope Leo X (1513) are now attributed to some poisonous effects of the varnish. In 1877, Senator showed that the whole surface of the body can remain covered with an impermeable layer for 8-10 days without any untoward effects, while animals with a larger cutaneous surface, with reference to the weight of the body, such as rabbits or horses, eventually die. In like manner, the damage done by extensive burns of the skin is not due to interference with cutaneous respiration and excretion of wastes, but to shock, changes in the blood and disturbance of temperature-regulation by destruction of the nerve-endings. The dependence of perspiration upon the innervation of the skin was discovered by Goltz in 1875 and shown by Ostromov and others to be associated with sudorific fibres in the sympathetic trunk and the spinal cord. The net result of the many experiments with atropine and pilocarpine upon the sweat-glands has been the establishment of the vagotonic and sympathicotonic diatheses and their relation to the sympathetic-autonomic system. That electrical impulses pass inward from the cutaneous glands was discovered by du Bois Reymond and confirmed by Rosenthal (1875). The cutaneous nerve supply for sensations of temperature, pain and pressure was investigated by Goldscheider (1884-5) and Max von Frey (1896). The problem of absorption by the skin occupied investigators during the whole of the 19th century. The difficulties encountered turned upon the varying reactions of the epidermis to different chemical substances, the unpredictable susceptibility or insusceptibility of different animals and different individuals and the fact that epi-

dermic reactions to many substances are negative. The classical instance, that of inunction by mercurials, was known even in the early Middle Ages. The best animal skin for absorption is that of the frog, as being in the nature of a perfect semi-permeable diaphragm. Skin-vision or the capacity of the skin of certain lower organisms to perceive light, has now been found to be true of the human skin with reference to colored light[6].

The functions of the skin have been neatly summarized by A. J. Hall[7] as follows:

1. The skin is our first line of defense against external injuries, including infection *vid* some solution of continuity. 2. It is also the body's outpost for heat regulation, the first tissue to be chilled or overheated by changes in external temperature. 3. It is the Intelligence Headquarters of the central nervous system and the sexual apparatus, being the first to contact with external agencies, good or bad, welcome or unwelcome. 4. Apart from the mucosa, it is the only tissue visible to other eyes, hence a principal medium for attraction, repulsion or evasion by protective mimicry. It is in brief, the universal receptor organ of the body. Where the unbroken cell membrane shoulders nearly all the business of nutrition and elimination, the only function of the skin in relation to the interior of the body is the excretion of water plus certain salts and as a heat regulator with regard to domestic metabolism. The skin is thus a screen or semi-permeable diaphragm between the external world and what is going on inside the body.

Early in the 19th century, as stated, the skin was regarded and referred to as a functional organ of the body; seldom, if ever, in the matter of cutaneous reactions to disease. In disease, the skin is not so much a protective covering as an organ. The more expanded concept is bound up with present knowledge of the relations of the parasympathetic and endocrine systems, the various serologic, allergic and pharmacologic tests, the effects of light, radiation and radium on the skin, its chamæleon-like sensitivity to atmospheric and emotional disturbances, all tending to the recent view that the skin is not so much the outward and visible index of internal disease as a very delicate reacting medium to pathologic stimuli from without and

[6] W. Finkler: *Umschau*, Frankfurt a. M., 1933, XXXVII, 213-215.

[7] A. J. Hall: *Lancet*, London, 1921, I, 426.

within[8]. There is a herpes which is fatal in pregnancy and a psoriasis which coexists with pregnancy, disappears at term and may reappear sometime after the birth of the child. Facts of this order illustrate the extreme lability of the skin with regard to happenings within and without the body.

One of the most interesting aspects of the skin as a reacting diaphragm is that of the application of therapeutic agencies to the surface of the body, of which we have familiar examples in hydrotherapy, with the capillaries as a kind of auxiliary skin-heart, cupping, leeching and venesection, counter-irritation by mustard plasters, the use of liniments, salves, mercurial inunctions, the seton and the moxa, massage and intradermal injections.

About 1793[9], Edward Jenner began to experiment with tartar emetic, and, confirming the experiences of Thomas Bradley (1773)[10] and John Ferriar (1792-8), found that eruptions produced by external inunction of tartar emetic salves would often abort certain diseases. By 1882, he had eighteen case histories[11], with evidence of relief in insanity, melancholia, asthma, nervous, respiratory and hepatic disorders and whooping cough, in which Robertson (*London Med. Reposit.*, 1821, XV, 6-12), had got phenomenal results. Jenner reasoned that the drug exanthem

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[8]For the skin as an organ, see, in particular: G. C. E. Sandrock: De cutis dignitate semeiotica. Marburg diss. 1831. A. Jesionek: Biologie der gesunden und kranken Haut. Leipzig, 1916. A. F. Hecht: Die Haut als Testobject. Wien, 1925. J. K. Mayr: Die Erscheinungen der Haut bei inneren Krankheiten. Leipzig, 1926. W. Grunow: Die Haut als Stoffwechselsorgan. Berlin, 1927.

[9]Jenner: *Tr. Soc. Improve. Med. and Chir. Knowledge*, London, 1793, I, 30-33.

[10]Bradley: *Mem. Med. Soc.*, London (1773-86), 1787, I, 247-252.

[11]Jenner: A letter to Charles Henry Parry on the influence of artificial eruptions in certain diseases incident to the human body. 4°, London, 1822. From the initial observation of Hippocrates on malaria and paralysis to the time of Coley (erysipelas in sarcoma) and Wagner-Jauregg, the nullification of one disease by another (*De morbis salutiferis*) had arrested the attention of physicians, particularly in the 18th century.

drove out the disease externally, each papule being a messenger of good news, as in small pox, and even proposed the treatment of all diseases by artificial production of skin-eruptions. It is known that vaccination will abort whooping cough and the prophylactic effects of the seton and the moxa were ancient history to the Chinese and the Japanese. The cutaneous aspects of syphilis, tuberculosis, the exanthematous fevers, the visceral neuroses, the gouty-rheumatic and neuro-syphilitic diatheses, and many other diseases, which have reduced the erythematous, purpuric, herpetic and eczematous eruptions to mere symptoms, may be regarded as the peripheral reactions of susceptible individuals to pathologic changes within the body. Allbutt, Charcot, Osler and Libman have shown that the multiform symptoms of certain diatheses, such as the gouty-rheumatic and neuro-syphilitic, may actually pivot in space and time around erythematous and purpuric eruptions by distribution among the ascendants, descendants and collateral sibs of a given family. On the other hand, the treatment of a limited, local cutaneous eruption will sometimes cause it to spread in an embarrassing way, and this is not due, as formerly supposed, to internal causes nor even to the skin itself, but to the reactions of its involuntary nerve supply in susceptible individuals. Idiosyncrasies to the primrose (*Primula obconica*), phenylhydrazin, quinine, and other chemical substances are innumerable and unpredictable. Hall's case of a widespread inflammation from knocking over a vase of roses containing a single primrose shows, in his view, a difference between specific, local, nervous susceptibility and allergy, which affects distant parts. An eruption from a necklace of pearls, was found to be due to a waxy substance within the pearls, affecting a patient found to be highly susceptible to greasy ointments[12].

The question arises, when does a cutaneous eruption indicate that the skin itself is diseased and when is it a sign of cutaneous activity as an immunizing or excretory agent, driving

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[12]Hall: *op. cit.*

the disease from within outward, as Jenner thought? One of the earliest manifestoes of the former case, the theme of most dermatologists up to recent times, is the curious pseudo-Hippocratic treatise, the *capsula eburnea* or Ivory Capsule, which deals with the prognosis of certain skin eruptions. That the skin itself has diseases all its own, can be powerfully affected by external agencies, from tropical sunlight, which produces a veritable furnace burn, to a pathogenic parasite, is self-evident. In 1918, E. F. Mueller[13] found that intradermal injections of the non-specific protein, aolan, in chronic gonorrhœa will produce remarkable therapeutic effects upon the distant urethral membrane, which cannot be duplicated by subcutaneous, intravenous or intramuscular injections; that a positive Wassermann can be superinduced in old syphilitics with a negative Wassermann by minute subdermal injections of a non-specific protein, and more recently that intradermal injections of insulin or iletin are in like manner, more potent than injections by the subcutaneous route. His conclusion, from later experiments, is that these remote effects are produced by a reaction of the parasympathetic fibres supplying the skin rather than by the particular substance, since a subdermal injection is negative. He reasons that the rôle of the skin in the Dick and Schick and von Pirquet tests, in asthma and idiosyncrasies to food, is that of a reflector of processes deviating from the normal. The toxins of diphtheria and typhus, as well as virulent bacteria, may be detoxicated by macerated bits of skin *in vitro*. The skin has therefore a direct immunizing action, as well as a remote healing action, like that in an intradermal injection of aolan, and this independently of the blood current and the blood cells; for none of these results are obtainable by intravenous injections.

Bruno Bloch, in 1917[14], produced a gradual and apparently perfect immunity from trichophytiasis by successive cutaneous vaccinations of the fungus. In 1927, he demon-

[13] E. F. Mueller: *Illinois M. J.*, Oak Park, 1925, XLVIII, 358-363.

[14] B. Bloch: *Cor. Bl. f. schweiz. Aerzte*, Basel, 1917, XLVII, 993-1007.

strated facultative susceptibility to *Primula,* and has since been the outstanding investigator of the allergies, anaphylaxes and idiosyncrasies of the skin.

That there is a powerful solidist immunizing property in the skin, apart from the humoral immunity attaching to the blood, may be taken as proved. It was called esophylaxis by Erich Hoffmann in 1919[15]. The assumption of some theorists that the skin possesses a specific internal secretion is best handled, for the present at least, by Occam's razor: *Entia non sunt multiplicanda,* since such extra hypotheses are footless, where a simpler explanation is available. The cutaneous manifestations of myxoedema, Addison's disease, gonadic disorders, pregnancy, puberty and the menopause are provisionally explicable by the relation of the endocrine organs to the sympathetic and parasympathetic nerve fibres. The allergic and endocrine reactions of the skin are legion. In Germany, patients susceptible to dust or allergy are kept in dust-proof, "allergy-free" rooms[16].

Long ago, Hebra, one of the great masters of his subject, said: "We are at present at our a - b - c's in dermatology and must learn to *read* the skin." Hebra, Da Costa and Joseph Bell, the original of Sherlock Holmes, were, in fact, able to amuse themselves by telling each of their patients, in succession, his occupation and other stray facts about himself, from a rapid survey of his external appearance. This sort of thing, like Corvisart's diagnosis of approaching fatality in heart disease from an oil painting, was an ambition of the period in which physicians had to sharpen their senses in default of instrumentation. Considerable information of an empirical kind has accumulated latterly, in connection with the revival of the doctrine of the constitution with regard to the external appearances of disease or tendency to disease. Cases in point are Kretschmer's studies of the cycloid or manic-depressive and the schizoid or praecox types and Draper's observations on the facial appearance

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[15]E. Hoffmann: *Deutsche med. Wochenschr.,* Leipz. and Berl., 1919, XLV, 1233-1236.

[16]A. Stühmer: Die Haut als vollwertiges Organ. Münster, 1931, 10.

of pernicious anaemics and victims of peptic ulcer. The earliest known representations of prehistoric man show that the body was covered by a more considerable amount of hair than latterly. Coarse, stiff, bristly hair is an almost infallible index of a strong, husky, full-blooded, thick-skinned, athletic make-up, where fine, feminine hair, a fair skin and so-called blue-blood, with a tendency to varix, connote the thin-skinned, anaemic or asthenic type. All abnormities of the hair imply weak or bad nerves. Loss of hair may connote syphilis (alopecia), hyperfunction of the thyroid (e.g., in pregnancy), phthisis or senility. The hairy skin of the virago (virilism) is an index of adrenal assertion and a scanty beard or moustache in male or female (*Altweiberbart*) implies weak or defective gonads. Hair prematurely gray is usually an effect of nervous shock or of the impact of environment upon an unstable nervous system. Red hair labors under the imputation of disagreeable aggression and duplicity in gaining selfish ends. People of the lymphatic or heifer-like temperament, with red or blonde hair, smooth white skin, freckles and blue eyes, are liable to tuberculosis (Hippocrates). Albinoes are prone to eczema. Dark (brunette) people are normally intensive and self-centred to the point of fanaticism in pressing a point and holding their own, securely sexed, better adapted to environment, to the tropics and to the impact of tuberculosis than blondes, who are more spontaneous and inconsistent, hence more liable to get into scrapes, through the restless, roving propensities of the Nordic (Havelock Ellis). The skin darkens in pregnancy. The signs of the choleric or apoplectic temperament are a sawed-off, chunky physique, a short wide chest, a full habit of body and a red face; while unduly bright eyes, a thin skin, with tendency to goose-flesh, profuse perspiration, tremor or even hæmophilia, indicate the labile, excitable, nervous and timorous natures. Degree of fatness, common to the pycnic or manic-depressive types, is regarded by Hoesslin as "a footrule of the constitution."[17] Furneaux

[17]Hoesslin: *München. med. Wochenschr.*, 1921, LXVIII, 797; 912.

Jordan regarded a vaulted back and a smooth, hairless face as an index of the male or female shrew, while the skin of the amiable, upstanding people, "courteous-eyed, erect and slim", has a certain amount of hair, down or *duvet*[18]. Hypothyroids and hypogenital types have a coarse, dry skin with defective perspiration, usually a sign of psychic instability. Hyperthyroids have continual perspiration and cold extremities. The German word for scabies is *Räude* or rough skin. Wheals on the body go with bronchial asthma and œdema. Extreme susceptibility to chemicals is regarded as a sign of the exudative diathesis, which is further liable to seborrhœa of the scalp, prurigo, pruritus, intertrigo and glandular enlargements. The dartrous diathesis of the French dermatologists connotes a tendency to herpes and eczema. In a lecture of 1832, Dr. Richard Bright outlined, as follows, the facial indices of the commoner internal disorders, whereby, in the old English idiom, the patient stands "in a bad skin":

"By the eye you will learn much; many diseases have the most distinct physiognomy. The sunk and shrivelled features derived from the long-continued disease of the abdominal viscera, the white and bloated countenance often attendant on changes in the functions or structure of the kidney, the sallow and puffy cheeks of the liver diseased from habitual intemperance, the squalid and mottled complexion of the cachexia dependent upon the united effects of mercury and syphilis, the pallid face of haemorrhage, the waxen lassitude of fever, the purple cheek of pneumonia, the bright flush of phthisis, the contracted features and corrugated brow of tetanus—all these shades of countenance and very many more which I might enumerate, with all their varieties of combination, are distinctly recognized by the experienced eye."

To "read the skin", with regard to the elaborate, colored illustrations in atlases of skin disease, is more the province of the professional dermatologist than of the clinician; but, in the light of recent knowledge, it is probable that even some of these readings may not be so simple as formerly. Like all external aspects of disease as altered physiology, they have been, in the convenient phrase of Pater, "liable from the first to an unobserved transformation."

F. H. GARRISON

[18]Jordan: Anatomy and physiology in character. London, 1886.

RECENT DEVELOPMENTS IN THE STUDY OF TUBERCULOSIS OF INTEREST TO PHYSICIANS*

WM. CHARLES WHITE

The tuberculous process in man and animals involves the living together of two independent organisms, the tubercle bacillus and the monocyte ameboid cell. Each of these has its own living chemistry. It would seem however as if they had certain common factors in their search for food supplies. Otherwise their close association in what we know as the tubercle would probably not be so universally found in the early history of the development of tubercles.

Under certain conditions with which we are at the present time little familiar, the living together of the two component parts of the tubercle may change in one of two directions, either the bacillus does not find a food supply adequate for its life and disappears from the scene, or it rapidly multiplies within the monocyte robbing the latter of its means of subsistence so that it dies and collections of these monocytes known as the tubercle coalesce and undergo a process known as caseation, in which substance the tubercle bacilli almost cease to exist as acid-fast rods but probably exist in some other form with a different chemistry. This caseous material then undergoes softening and usually ruptures from its surrounding environment. At this stage the acid-fast form of the organism begins again to appear. If the rupture takes place to the outside of the body and the acid-fast organism is fortunate enough to find new hosts then it goes through the same cycle. If the rupture is into some cavity or vessel within the body then the organism goes through the same process that has just been described in another part of the same body. This conjugate life of these two living cells along with the de-

* *Delivered before The New York Academy of Medicine, March 10, 1933, in the Friday Afternoon Lecture Series.*

velopment of new methods of study in the laboratory has opened the door for a new attack on the tuberculosis problem.

I might interject here that the tuberculosis problem in all its ramifications is the most expensive disease problem with which man has to deal. The individual case is the most trying with which the practitioner of medicine has to deal and with our present methods it is a long discouraging problem both for the patient and the physician.

Taking now the two living factors that go into the formation of the tubercle I would first bring your attention to what we know of the monocyte or host cell and what methods are available for studying its life history and then describe to you the modern attempts in chemistry and biology to study the tubercle bacillus or infecting parasite, and thirdly, describe the influence of these studies on modern thought in connection with patients suffering with this disease. Before doing this I would like to state that the Director of The New York Academy of Medicine, Dr. Linsly Williams, has been an interested participant in these studies from the beginning.

The monocyte cell is an independent ameboid cell and one of the component cells of all vertebrate animal bodies. Within the body it has three possible forms of motion:

1. Inherent power of moving by ameboid action from place to place.
2. Movement by the blood stream.
3. Movement by lymphatic flow.

In the development of vertebrates the monocyte appears first by differentiation of cells from the mesoderm. Part of the mesodermal cells become angioblasts, giving rise to the endothelial lining of vessels and part of them remain outside this lining to develop into what is known as fixed connective tissue cells and these are apparently able to develop into monocytes or clasmatocytes or fibroblasts under the influence of certain environmental stimuli. In

those animals which have been carefully studied, however, their main place of origin, in the fully grown animal, is in the connective tissues. They also arise in the lymph glands which, as you know, are a frequent site of tuberculosis. Cells very similar to them are produced also in the pulp of the spleen and appear in greater abundance in the splenic vein which flows directly into the portal vein going to the liver.

Amebas in nature tend to round up and rest at certain periods of their life history. Their food supply is largely bacteria. Under certain conditions they develop what is known as multi-nucleosis. That is their nuclei divide without the whole cell body dividing. In this condition they are known to us as giant cells. Monocytes in the body tend to form a similar type of giant cell in the tuberculous nodule. Their specific functions in the body are yet undecided problems. This much, however, seems certain—that they have in some way to do with the utilization of certain classes of fats and it is in this point of their function that we will probably find their chemical relation to the tubercle bacillus, which under proper conditions can grow so abundantly within the body of these cells. One fact stands out—that in neither the tubercle bacillus nor in the monocyte is there evidence that the sterols, such as cholesterol, are an important step in whatever their chemical function in connection with the fats may be.

One of the great difficulties in studying the living chemistry of the monocytes is the lack of a method to obtain them in pure culture, although it is possible that the recent method described by Rous and Beard in which they load the Kupffer cells with iron and then withdraw them from their normal environment in the liver by an electric magnet may bridge this gap in our technique.

An easier field of study from the standpoint of living chemistry is offered by the tubercle bacillus. This can be obtained in pure culture and even a pure culture developing from a single cell. This culture can be produced in great

quantities on a constant medium, it can be extracted by various solvents and the extracts from these solvents be produced in sometimes pure and crystalline form and the effects of these pure substances tried on the living normal and tuberculous animal. One of the difficult problems however in this procedure is that tubercle bacilli are members of a vast family known as the acid-fast family and the number of strains in this family, each with its peculiar chemistry, increases so rapidly that the work of analysis seems almost endless. This much however can be said, that whenever any member of this family is introduced into the animal body it always, whether it produces disease or not, has some relation to the monocyte cell. If it be a virulent strain it will rapidly multiply in these cells as the beginning of the disease process, and if it be avirulent it soon ceases to exist in the body.

For the past seven years a group of students, many of them here in New York and members of the Academy, have been interested in the study of the chemical fractions that can be isolated from the different strains of tubercle bacilli and the influence of these on the animal body. I may mention among these Dr. R. J. Anderson, Dr. Sabin and her associates, Dr. Heidelberger and Dr. Kendall, Dr. Long and Dr. Seibert, Dr. Richardson, Dr. Loebel, Dr. Shorr and Dr. Kahn.

The substances which have been isolated belong to the proteins, the phospho-lipins, the waxes and the carbohydrates. For the isolation of these substances five strains of acid-fast bacteria have been used. They have all been grown upon a common medium and a careful comparison drawn between the quantities of the substances which each different strain produces. These bacillary strains are human, avian, and bovine tubercle bacilli which are virulent, and two avirulent strains.

Such substances as have been so far isolated are common to all strains but there are very large and significant differences in the quantities of a number of these isolated

substances that each strain of organism produces. This is especially striking in the carbohydrate and phospho-lipin fractions and one may say that as the phospho-lipin increases the carbohydrate fractions decrease and vice versa. Two great objectives are sought by the analysis of these bacterial strains. First, there is the hope that we may find a law in synthesis sharply demarking the virulent strains from the avirulent strains and that by knowing the law which contributes to virulence in a bacterium we may, by introducing some substances into the body, break the chain by which a bacillus may continue to grow and kill an animal. This breaking of the chain may be conceived of in simpler terms, as, for example, starving the bacillus or enriching the powers of utilization of food supplies by the monocyte. You will readily realize that this is quite different from the old thought of chemotherapy as developed by Ehrlich in which a dose of a drug fatal to the invading parasite but harmless for the body cell was the goal. This type of therapy is exemplified by the use of arsenic and antimony for trypanosomes and treponemata and by quinine for the malarial parasite. Such a method is probably not applicable in tuberculosis. In trypanosomiasis and spirochætosis the invading organisms have their life quite outside of the cells of the body. In malaria there is an extra-cellular cycle of the parasite during which its death is brought about, but the intracellular life history of the tubercle bacillus within the monocyte is quite a different story. Secondly, by knowing the physiological effects of introducing the fractions of the bacillus into the body it seems possible that other substances may be developed of known chemical activity which may be introduced into the body and stop the destructive processes of the life of the parasite—such destructive processes for example as caseation and softening of the large tuberculous aggregation of cells.

There are now known to be several proteins in the tubercle bacillus family. Some of these, when introduced into the normal animal body in their undenatured form,

produce results similar to those produced by all natural foreign proteins. This has been beautifully shown by Dr. Sabin, Dr. Seibert, and others. The animal for instance becomes both anaphylactic and skin sensitive to the reinoculation of the same protein at a later time. This protein is common to all the acid-fast family and will undoubtedly have some definite bearing in the final use of our diagnostic test known as the tuberculin test.

A curious state of affairs has been found in rural Minnesota where the skin of children living upon farms has been more sensitive to this undenatured protein from the timothy grass bacillus than that from the tubercle bacillus.

After a careful study of the literature of the early experiments of Koch with tuberculin on which he based his proclamation of a cure, it seems to me the story is something like this. When he used his first extracts of tubercle bacillus on guinea pigs and got such favorable results he probably was using the unheated extracts and therefore was introducing protein with definite antigenic power, but when he was forced to use his extracts on human beings he found it necessary to boil his extracts and thus spoiled the antigenic power of his proteins and from that time onward, tuberculin has been a boiled product and devoid of antigenic properties. It seems possible that a new era may be approaching in which experiments will be carried on with undenatured proteins of the bacillus which possess this antigenic power and probably a reconstruction of our view about the value of the extracts of the tubercle bacilli in curative medicine. In other words I think Koch was unfamiliar as we all have been with the fact that heating the unchanged protein of the tubercle bacillus destroys its antigenic value and possibly its curative value.

The general result of our studies on the pure proteins of the acid-fast family has been the production of a substance for the testing of skin-sensitiveness in the tuberculous which in the first place can be quantitatively diluted

and it is our hope that secondly it can be so diluted in solution that it will give a specific skin test for the presence in the body of virulent bacilli and perhaps we may even hope a specific test for a given strain of bacillus. One sees in the modern use of tuberculin, a procedure quite contrary to all our other good biological tests in that we proceed by increasing the amount of tuberculin until we get the maximum number of reactors rather than a procedure of diminishing the quantity until we get an evidence of specificity which would be of real diagnostic value.

The physiological action of this undenatured protein in the normal animal and in the tuberculous animal has been carefully worked out by Dr. Sabin and her associates. One of the specific cellular responses in the normal animal to the undenatured protein has been found in the study of Dr. Franklin Miller who has been able to work out the differentiation and production of one of the rare cells of the body known as the plasma cell. The influence of this protein on the temperature of the body, on blood pressure, on injury to endothelial cells and the central nervous system has been carefully studied by Dr. Sabin and Dr. M. I. Smith. The work in this field is still progressing very rapidly under Dr. Seibert looking towards the determination of the size and chemical structure of the molecule responsible for each of these physiological responses.

With our present knowledge it may be said that, in general practice in testing with tuberculin in man and animals, a positive tuberculin test is the evidence of some member of the acid-fast family growing in the body. It is not proof that this is a virulent member of the group and our studies will not be complete until we have a diagnostic substance for testing that will answer this question.

If we increase the quantity of the undenatured protein of the timothy bacillus we obtain the same reaction as that obtained from a very minute quantity of the protein obtained in the same way from the bovine bacillus. The protein obtained in our studies from the bovine strain is by far the most potent for this type of reaction. That is it

requires less of it than of the protein from any of the other strains. We have no satisfactory explanation to offer of this fact.

The Phosphatide Fraction

The fatty fractions of the tubercle bacillus have been separated by their solvents into several well-known groups such as, for example, an acetone soluble fat, a phosphatide, and a chloroform soluble wax. Early in these studies it was found that the so-called phosphatide, a phosphorus containing lipin combined with a polysaccharide, had the property, when introduced into a normal animal, of stimulating the multiplication of the monocyte cell thus probably bringing this fraction into a close chemical relation with the chemical function of this cell in the body. This phosphatide is taken up by the monocyte cell and digested slowly. The monocyte cells containing the phosphatide pack together much as they do in tuberculosis and if the dose be large enough they coalesce and undergo caseation. This change to caseation is enhanced by the introduction at the same time of the undenatured protein fraction referred to above. This property which the phosphatide possesses has been found by further analysis to belong to an optically active fraction of the phosphatide named by Anderson "phthioic acid". It is a common substance in all strains. The production of this material by the growth of the living bacillus outside of the body and its action upon cells of the body after death of the bacillus is undoubtedly related in causation to two of the prominent processes present in the natural disease. The work of providing substances which may interfere with these processes of the massing of monocyte cells and coalescence and caseous change, is surrounded with so many difficulties that up to the present very little progress has been made. As new methods appear and more knowledge accumulates it seems possible that a door will be opened to offset one or other of these most destructive chemical actions which accompany tuberculosis.

It is a remarkable thing that this family of bacilli should have the power to build from a simple medium such an

amount of phospho-lipin in combination with such a complex polysaccharide. The importance of phospho-lipin in all living cell activity has of late years been growing very rapidly. One may say that wherever life occurs these phospho-lipin sugar combinations stand out as an integral necessity in life activity. One is presented in the tubercle bacillus growth on a simple medium with an opportunity of studying the mechanism by which synthesis of phospholipins occurs, and the intermediate products which are established in the conversion of glucose into fatty acids and their later combinations with glycerol and phosphorus to form some higher straight chain compounds of carbon. Anderson's masterly work in demonstrating the power of this family to produce a fatty acid of twenty-six carbon atoms in chain is among the great achievements of modern bacterial chemistry. In this phosphatide fraction he has already shown the presence of butyric acid with four carbon atoms, palmitic acid with 16 carbon atoms, and stearic, linoleic, and linolenic acids with 18 carbon atoms. When one attempts to correlate this with the function thought to occur in the synthesis of fatty acids in the perfused liver from salts of pyruvic and lactic acid and the probability of further synthesis in the liver and lung, synthetic functions that may be in part inherent qualities of the monocyte cell, it is possible to let the imagination run to the belief that there is close relation in the synthetic chemistry of these two living cells and that when we understand it we may be a long way on our journey towards a cure of tuberculosis. But this is no place for imagination and I must recount only the facts as we now know them.

Waxes

The waxes which have been isolated from the bacilli produce lesions of so complex a character, when introduced into the normal animal, that little can be said at this time of their function. The waxes have, as you know, in the past been variously considered as the most important part of the bacillus. The literature is full of statements about the "waxy capsule" but so far as our studies are concerned,

there is not the slightest evidence that the wax forms a capsule rather than being part of the body of the bacillus. The wax from the tubercle bacillus is a higher alcohol. There is no evidence that waxes in nature take part in the vital processes of the living organism. They are rather protective in character against the action of water and other penetrating and degrading agents. When injected into the body this wax induces the multiplication of connective tissue cells which fuse to make foreign body giant cells around the particles. Thus, with reference to the lesions of the disease, this reaction may be considered as non-specific.

Sugars

The significance of sugars in combination with proteins and lipins in living chemistry has tremendously increased in the last few years largely through the studies of Avery, Heidelberger, and Laidlaw and Dudley. That there should be so vast a difference in the biological activity caused by the spatial difference of one hydroxyl group in a molecule, as shown by Avery and Goebel, and that there should be a difference of 10 times in the physiological activity of codeine and pseudo-codeine with only the spatial difference of one hydroxyl group in the molecule is so significant of the importance of these simple chemical differences in physiology that one has to restrain oneself in picturing the future of accurate chemical, biological knowledge.

And yet Emil Fischer, the father of modern carbohydrate chemistry, did not hesitate in his address before the German Chemical Society in 1890 to let his imagination run in these words:

"Next to the albumens the natural carbohydrates form the chief food stuff for the animal kingdom, especially for graminivorous animals, and a large number of valuable observations have been made concerning the processes they undergo in the animal body. Might it not be possible to substitute some of the artificial sugars for these natural carbohydrates, and what would be the result? Mannose so closely related to grape sugar, and so easily fermented by

yeast, might very probably form a good foodstuff, even for the more highly organized animal; and yet the slight change of substance might cause corresponding changes in the vital processes. If mannose be taken as food, will the liver produce a new glycogen, and the mammalian gland a substitute for milk sugar; and will this sugar be oxidized in the body of the diabetic? The changes in the animal organism could not but be still more decided, if one could succeed in feeding the animal body with a pentose or a heptose, or the easily fermentable nonose. One would then probably find that blood and tissues would modify their functions, that the pig and the goose would produce a changed fat, the bee a changed wax. Indeed the experiment might be carried still farther. The assimilating plant prepares from sugar not only the more complicated carbohydrates and the fats, but also, with the help of inorganic nitrogenous compounds, the albuminoids. Certain classes of bacilli have the same power. Now, if it were possible to feed the assimilating plant or these bacilli with a differently constituted sugar, they might possibly be forced to form a changed albumen. May we not then expect that the changed building material will lead to a changed architecture? We should thus gain a chemical influence on the formation of the organism which would necessarily lead to the most extraordinary phenomena, to changes of form far exceeding all that has been reached by crossbreeding, etc. Since the fundamental experiments of Wholer and Frerichs, physiological chemists have incorporated hundreds of organic substances with the animal body, seeking the products in the urine; but they, almost exclusively, made use of substances having no likeness to natural foodstuffs. The use of the new series of sugars offers a wide field of action to the physiologist, and may be attended by results far more extraordinary. Biology here stands before a problem, which has never yet been set, nay, which could not have been set until chemistry had prepared the material for the experiment."

Early in the history of these studies it was shown in England and in America that the crude polysaccharides of

the tubercle bacillus family had immense power of causing a precipitate when brought into contact with the serum of animals injected with the whole dead bacillus. I was able to show, by using one of Anderson's polysaccharides found in union with the phosphatide fraction, that there was a profound influence on the temperature and blood pressure and in the distribution of the lipin substances in the cortex of the adrenal glands, when this polysaccharide was injected into the tuberculous animal. The relation of the adrenal cortex to blood pressure and temperature has been emphasized by Cannon and by those working with extracts of this part of the gland. Dr. Sabin has made a careful study of the blood changes produced in the normal animal by use of the same substance. It is very destructive to polynuclear leukocytes. While we know it is such a poison we have so far been unable to demonstrate it in the serum of the tuberculous animal. We are sure that it must be there in some masked form. We feel sure also that it has some definite relation to the daily temperature curves of the very sick animal. Of late months there has been a growing belief that there is a daily death of a generation of tubercle bacilli in the advancing tuberculous animal coupled with the release by lysis of this poisonous substance which may be the underlying cause of the febrile cycle and that if it were possible to demonstrate its presence and cause its destruction there might be one method of controlling one of the most distressing symptoms of tuberculosis. This polysaccharide is a very stable substance requiring boiling with acid to break it up. When broken up it yields such simple sugars as mannose, inosite and d-arabinose. These simple sugars when injected into an animal have no biological significance nor do they have any influence, when put in the medium in the test tube, on the growth of the bacillus. It is only when they are united with phosphorus and nitrogen in a stable polysaccharide that their poisonous effect is produced. This poisonous polysaccharide has no influence on the normal animal and when injected appears in the urine unchanged so that one is forced to the conclusion that the tuberculous animal develops a mechan-

ism which operates in conjunction with the polysaccharide to bring about the death of animals in a few hours.

To carry farther a report of these studies which have been carried out under the Committee on Medical Research of the National Tuberculosis Association would lead us into the intricacies of chemistry and biology that would not be suitable for those not intimately and daily in association with these sciences. I trust in presenting them to you and attempting some correlation of their findings that I may have indicated to you the trend of modern research, using new implements of study, and aroused in you the hope that is in us that we may, by pursuing them, achieve the knowledge which will put in the hands of the physicians implements effective in the control of the disease in the individual patient and enable us, as a people, to control the disease which takes so great a toll of our young adult life and of those animals which we use for the maintenance of our life.

THE BULKLEY LECTURE

THE CARE OF THE CANCER PATIENT*

(ABSTRACT)

DOUGLAS QUICK

The many and varied problems confronting the family physician relative to the cancer problem extend from cancer prevention and early diagnosis to decisions on treatment measures, embracing frequently the very trying terminal care of the case in which those measures have failed. The physician in general practice sees, on the average, only three to four cases of malignant neoplastic diseases per year. He cannot be expected to be familiar with all the varied phases of allied diseases under the general heading of cancer.

The term "cancer" covers the entire field of malignant neoplasms—indicating a group of diseases allied by virtue of a common characteristic. That group of diseases is the largest in the entire field of medicine. A calm well-balanced appraisal of the actual condition should be made. The fact that some groups of malignant diseases are curable, ranging from 70 per cent to 90 or 95 per cent, is lost sight of. The gradual improvement in clinical therapeutic measures and the improved palliative measures of the past decade for the ultimately incurable are important factors. The desirability of the careful periodic health examinations by the public with the attendant recognition of pre-cancerous and early malignant manifestations cannot be too strongly urged.

Pre-cancerous Manifestations: In the light of our present knowledge of neoplastic diseases it is not enough to accept responsibility for the care of the fully developed cancer only. Many may be and can be avoided. It is true that we do not know the cause, or causes, of cancer, and more

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* *Delivered before The New York Academy of Medicine, March 31, 1933, in the Friday Afternoon Lecture Series.*

than probable that this generation will be denied the secret, if such there be. We are familiar, however, with many "contributory" causes; we recognize certain "pre-cancerous" lesions. The removal or care of these is usually simple, and while not as spectacular as the cure of an established malignant growth, is in many respects more important because of relative numbers involved. The prevention of cancer by removal of a contributory exciting cause, or removal of a tissue bed (the seat of chronic inflammatory changes suitable for the development of new growth) is as much to be commended as the control of the fully developed lesion. It is by such preventive measures that true cancer control will become effective. It is only through a very substantial grasp of the entire problem by the general profession that warning signs and preventive measures will be recognized and acted upon.

In the development of malignant disease chronic irritation of tissues is a recognized contributory factor. In simple forms, this is noted on skin surfaces irritated over a period and remaining so, and is particularly true with respect to wind and sun burns; dermatoses resulting from certain industrial work in the use of drugs, or on the basis of old x-ray and radium burns of radiological workers. In addition, there are the small congenital abnormalities, warts and moles, subject to chronic irritation or degenerative changes later in life.

As a contributory factor, poor oral hygiene is most definite and pronounced; rough and irregular teeth; poorly placed fillings; neglected dentures and ill fitting plates. Over a period of years the contour of the bones of the face changes and the wearing of the same plates for many years without readjustment is a frequent source of chronic irritation. Dentists, as a group, are keen to recognize many of the early changes in the development of new growths, but many confine their activity to direct repair of teeth, and overlook the patient's general oral hygiene. Excessive smoking plays a part as a contributory factor. The relative sensitivity of the mucous membrane varies in different

individuals. Hence, it is the excess of one's individual tolerance which does the harm. The persistence of a heavy coating on the tongue is capable of far-reaching effects. As a bacterial culture-medium it excels and contributes to the infection and the reinfection of the lymphoid tissue about the pharyngeal ring.

There is no specific relationship between syphilitic manifestations within the mouth and the ultimate development of cancer. Again, as in the case of x-ray dermatitis of the skin, a suitable tissue bed is furnished for a new growth. The influence of oral sepsis on the upper digestive tract in the subsequent development of cancer is far underestimated. Simple factors of daily care of the mouth come under the eye of family physician and dentist and are too frequently overlooked. It is a duty to insist upon proper recognition of this phase of preventive medicine by their patients. With proper attention and cooperation intra-oral cancer can be largely avoided.

Pre-cancerous lesions and contributory factors toward new growth in the breast are less clearly defined than those referred to. However, many of the chronic inflammatory processes in the breast must be regarded as ultimately hazardous in a certain percentage of cases. Whether the irritation be a result of faulty drainage, the trauma of hypodermoclysis needles, the scarring from drainage of breast abscesses, or the periodic bleeding nipple, the condition at least demands the treatment that would be accorded a low-grade inflammatory process elsewhere.

Unusual uterine bleeding, particularly any bleeding beyond the menopause, is too well recognized to call for comment. However, the conditions which so frequently precede the cardinal evidence of new growth are overlooked entirely. Old lacerations of cervix uteri, with inflammatory exudates irritating surrounding tissues, are ignored. Faulty drainage of secretion from the fundus uteri is a source of chronic irritation and inflammation. Observations on races and classes of people with differing habits point clearly to the fact that every-day personal cleanliness

in habits has considerable bearing on the percentages of carcinoma of the cervix.

We have little specific information as to definite contributory causes which may be looked for or avoided on the part of the physician in connection with the upper gastro-intestinal tract; that is, from the esophagus to the small bowel. Varying degrees of sensitivity in different individuals make the matter of irritation from differing types of food a relative matter. That oral sepsis may be of greater importance than the character and temperature of food taken is worthy of consideration and investigation. In the colon and lower bowel certain anatomical abnormalities are of significance. Polypi and diverticula are potential points of irritation and inflammation. Rectal bleeding should be taken seriously. A diagnosis of hemorrhoids should never be accepted without eliminating the possibility of new growth. In following the gastro-intestinal tract, the clinician should be advised against too much reliance on negative x-ray findings in the lower bowel. The relative value of this diagnostic method is much greater in the upper tract than in the lower.

Diagnosis: The vital importance of early recognition cannot be stressed too strongly. Unfortunately, too many diagnoses are made entirely too late. Cancer should be regarded as a large group of closely allied diseases. Routine health examinations, carefully and seriously done, will contribute greatly toward early diagnosis of many malignant growths. Complete examinations of the patient will advance and simplify the general problem of cancer diagnosis. Present developments in x-ray and laboratory aids allow little excuse for overlooking new growths in a routine examination. The resort to biopsy should, of course, always be determined upon reasonably. The fact remains that when in doubt, biopsy will do far less harm than leaving a malignant growth to establish its own diagnosis. Tissue removed for section need not be large. Trauma of surrounding tissues should be avoided.

In the consideration of tertiary syphilis in the differential diagnosis of many tumors, particularly those presenting an ulcerating surface, a positive Wassermann must not be taken as conclusive that the lesion is undoubtedly luetic. Biopsy should be resorted to if the clinical picture is at all questionable. Too frequently the possibility of cancer is ignored because of the positive blood reaction.

Treatment: The treatment of any malignant growth might well be considered under one of the following headings: Curative, palliative, or psychological. If there seems reasonable opportunity for complete eradication, then measures for the treatment of that particular case ought to be exerted to the limit. If palliation only is possible, every consideration ought to be given the patient's comfort from day to day. Considering the entire field of malignant disease, from simple rodent ulcer (probably 95 per cent curable) to osteogenic sarcoma and active melanoma, the average of actual curability for the entire group of malignant neoplastic diseases is probably not more than 30 per cent. A large group is left in which palliative treatment comes to be a last resort. The manner in which these are handled from the psychological standpoint is most important.

Specific Therapeutic Measures: As far as the active and direct treatment of new growth is concerned, it is almost entirely surgical, operative or otherwise. The only agents at our disposal at the present time for direct treatment are surgery, x-ray and radium. Surgical technique has reached a high state of perfection. The technical procedures incident to the application of x-rays and radium are improving, still the use of these physical agents is of such recent date that much more can be expected than has been accomplished in the past. It is in the combination of these agents with the benefits of conservative surgery that most may be expected in the future treatment of cancer. Through the assistance of radiation, the character of present day cancer surgery has been decidedly altered. Surgical procedure has been rendered safer by radiation in some of

its forms, as well as limiting the necessity for some of the spectacular and extensive operative procedures attempted in a heroic effort toward controlling a more advanced type of disease. If the disease be advanced to such an extent that complete removal is not assured, or if the general physical condition of the patient does not warrant an extensive operation, the benefits to be derived from radiation are such that the surgical steps may well be replaced by the other methods. Preliminary irradiation, followed by surgical removal, affords the patient a better chance for ultimate cure. An otherwise unsuccessful operation may be turned into a successful procedure by resorting to the implantation of radium emanation to care for that portion of the growth which cannot be safely extirpated. There should be no confusion as to the relative places of x-rays and radium in the treatment of cancer. X-radiation may be employed only for external application and for the most part over large areas. Radium, on the other hand, lends itself best to application within body cavities, over localized areas, and, most important, for direct implantation within the tissues. There is some difference, however, between the gamma rays of radium and the hardest x-rays obtainable with our present high voltage x-ray equipment. It is true that if adequate quantities of the radiation from both sources are available for comparison, the gamma rays are more effective and efficient than the best that can be produced through an x-ray tube at this time. The possibilities of the future development of x-ray therapy strongly suggest that the surface has only been scratched in the ultimate development of this type of radiation. The work in histological grading of tumors bears a relationship to the relative radiosensitivity of tumors to irradiation. The two are not in parallel. However, they serve collectively as a valuable guide in the selection of treatment methods. The fully differentiated tumors, slower in growth, less liable to secondary dissemination, are more resistant to a given quantity of radiation and it is here that surgery offers most. Anaplastic growths, tending to metastasize early and at distance, with control by extirpation slight, are fortunately

much more radiosensitive and consequently more dependent on irradiation. Beneficial effect of radiation from a therapeutic standpoint is not limited to effect on tumor tissue alone. It is quite possible that the effect on surrounding normal tissues (aptly called the tumor bed) is as important as the direct effect upon the neoplasm. The problems incident to the combination of these various methods and application to individual cases, call for special facilities and special training. This does not mean that the cancer patient should be taken away from the family physician; rather, that the special equipment and special training necessary in meeting the problems be made accessible to him who must after all carry a very considerable portion of the burden.

Constitutional Measures: Malignant diseases may and do exist in conjunction with many other grave medical conditions. Cardiorenal disease, diabetes, tuberculosis, must be cared for just as carefully, or more so, in the presence of cancer as at any other time. No strenuous therapeutic procedure, operative or otherwise should be undertaken for cancer without a careful appraisal of the patient's general physical condition quite apart from the immediate problems incident to the malignant condition. The opinion of the internists will naturally vary as to the relative value of types of supporting medication, but whether it be the administration by mouth of stimulants to digestion; intramuscular medication with iron and arsenic; stimulation of body surfaces by means of the quartz lamp — all measures that will aid to maintain the patient's general physical condition should be resorted to. The advances in the therapy of anæmias may well be taken advantage of. Liver extract and iron are almost as much a blessing to cancer therapy as in pernicous anæmia itself. The cancer patient is hanging for support on every bit of encouragement. A great deal of value is to be derived from various measures in a psychological way. Whether benefit is physical or mental the result obtained is justification for the means. The statement is incorrect that antiluetic treatment of a patient with both

syphilis and cancer is contra-indicated if treatment by irradiation is employed. It is true that aggressive irradiation treatment of the malignant growth is a very severe strain on the constitution of any patient. It is likewise true that aggressive antiluetic treatment is a considerable strain on certain organs. It will be found, however, to enhance rather than damage the irradiation response. It is advisable to save all possible time by treating the malignant growth as soon as recognized, supported by a moderate course of antiluetic treatment, completing the antiluetic treatment consistent with patient's recovery and physical ability to stand the strain. The two diseases may well coexist. It is wise, if there is uncertainty from the clinical standpoint, to go beyond the positive blood reaction and substantiate the diagnosis of granuloma or neoplasm by histological tissue examination. The damage incident to taking a small piece of tissue is negligible. The time saved in beginning adequate treatment is of inestimable value.

Palliative Treatment: This may be regarded simply as those measures incident to carrying the patient along. However, it would be better to consider it as treatment actively and seriously carried out toward the relief and control of symptoms. Prolongation of life is rarely justifiable unless attended by a degree of relief from pain and the unpleasantness of irritating discharges and foul odors. Opinions may differ as to the relative values of radiation as a curative agent, but there is little doubt as to its value as an efficient control of these symptoms. Any reasonable and worthwhile palliative operative procedure, adding to the physical and mental well-being of the patient, though in no way curative, is advisable.

The cancer case usually is of long duration and in the use of sedatives the utmost caution should be exercised. A sharp distinction should be drawn between actual pain and restlessness following a period of pain. Vigorous cleansing measures will do a great deal to lessen the need for sedatives. Frequent, careful irrigations with mild antiseptic solutions are of value as a substitute for sedatives. Physical

measures, such as hydrotherapy, phototherapy and chemotherapy should be used to avoid drugs. The type of pain in many malignant cases is relieved better by salicylates than by opiates. A combination of salicylates with codein is far more advantageous than codein or morphine alone. Even under adverse circumstances a ½ gr. codein with 10 grs. aspirin will give relief for a period of several hours. Morphine should be carefully avoided and employed only as a last resort for relief in the terminal stages of the disease. The use of cocaine regularly on painful surfaces is extremely dangerous, even over a short period of time, because of the amount of absorption with the deleterious effect on the patient.

The Family Physician: The physician who devotes himself largely to the care of malignant diseases too often criticizes the family physician's errors, particularly in the establishment of diagnosis and getting treatment under way. It would be much better for the specialist to give more time to further the family physician's knowledge of the problems associated with the active treatment of the patient. The family physician is better acquainted with the patient and the family and is in better position to maintain the morale of both. His active participation in the care of the case permits of the proper relationship and dignity which is the right of the general practitioner. If the specialist and the family physician keep each other thoroughly advised, each will accomplish his part of the work to the better advantage of the patient and the family.

LIBRARY NOTES

Recent Accessions to the Library

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Roma, Pozzi, 1932, 291 p.

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Torino, Lattes, [1933], 240 p.

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Prinzhorn, H. Psychotherapy: its nature, its assumptions, its limitations.
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Sands, I. J. Nervous and mental diseases for nurses. 2. ed.
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Scritti medici dedicati a Riccardo Simonini nell XXV di suo insegnamento.
Modena, Tip. "Immacolata concezione," 1932, 913 p.

Souttar, H. S. A surgeon's pocket book.
London, Heinemann, 1933, 285 p.

Viola, G. La costituzione individuale.
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Ward, W. R. & Smith, A. J. D. Recent advances in radium.
London, Churchill, 1933, 324 p.

Wehlau, M. Frontzahnbrücken bei lebenden Pfeilern. 2. Aufl.
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Weil, A. A text-book of neuropathology.
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A Selected List of New Periodicals Added in 1933

(January to June)

Acta brevia neerlandica de physiologia, pharmacologia, microbiologia e. a.
Amsterdam, vol. 1, no. 1, Mr 1931.
Archivio italiano per le malattie della trachea-bronchi esofago.
Parma, vol. 1, no. 1, Ja/Mr 1933.
Archivos uruguayos de medicina, cirugía y especialidades.
Montevideo, vol. 1, no. 1, O 1932.
Brompton hospital reports.
London, vol. 1, 1932.
Cirugía ortopédica y traumatología.
Habana, vol. 1, no. 1, Ja 1933.
Folia ophthalmologica orientalia.
Jerusalem, vol. 1, no. 1, N 1932.
Hippocrate; revue d'humanisme médical.
Paris, vol. 1, no. 1, Mr 1933.
Medical forum.
London, vol. 1, no. 1, N 1932.
Medico-legal and criminological review.
London, vol. 1, no. 1, Ja 1933.
Monatsschrift für Krebsbekämpfung.
München, vol. 1, no. 1, Ja 1933.
Revue française de puériculture.
Paris, vol. 1, no. 1, Mr 1933.
Revue médico-sociale de l'enfance.
Paris, vol. 1, no. 1, Ja/F 1933.
Rivista italiana di psicoanalisi.
Rome, vol. 1, no. 1, Ja/F 1932.
Royal Berkshire hospital reports.
Reading, England, vol. 1, 1932.

Hours During the Summer

From June 15 until September 15 inclusive, the Library will be open on week days from 9 a.m. to 5 p.m., on Wednesdays from 9 a.m. to 10:30 p.m., and on Sundays from 10 a.m. to 5 p.m.

DEATHS OF FELLOWS OF THE ACADEMY

RICHARD TRAVIS ATKINS, M.D., 4 West 53 Street, New York City; graduated in medicine from New York University and Bellevue Hospital Medical College, New York City, in 1906; elected a Fellow of the Academy February 3, 1921; died, June 27, 1933. Dr. Atkins was a Fellow of the American Medical Association, a Fellow of the American College of Surgeons, a member of the County and State Medical Societies, a member of the American Otological Society, the American Laryngological Society, the Otological Society, the Laryngological Society, the Society of Alumni of Bellevue Hospital, a member of the Society of Alumni of the New York Eye and Ear Infirmary, Surgeon in charge of the Ear, Nose and Throat Department of Bellevue Hospital, Surgeon to New York Eye and Ear Infirmary, Consulting Otolaryngologist to Hackensack Hospital, North Country Community Hospital, Glen Cove, and St. Agnes Hospital, White Plains.

L. MILLER KAHN, M.D., 29 East 93 Street, New York City; graduated in medicine from the Memphis Hospital Medical College, Memphis, Tennessee, in 1900; elected a Fellow of the Academy April 4, 1912; died, June 24, 1933. Dr. Kahn was a Fellow of the American Medical Association, a Fellow of the American College of Surgeons, a member of the County and State Medical Societies, a member of the Society of Alumni of Lebanon Hospital, and Surgeon to Lebanon and Beth David Hospitals.

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